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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/047,652	03/25/1998	VASSILIOS PAPADOPOULOS	009/064/SAP	3470

909 7590 12/27/2004

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/047,652	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-68 and 70-80* is/are pending in the application.

4a) Of the above claim(s) *58-63 and 66-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-57,64,65 and 70-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 70-80, which are related to claims 53-57, 64-65 and are not new matter.

Accordingly, claims 53-57, 64-65, 70-80 are examined in the instant application.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 53-57, 64-65, 70-80 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 53-57, 64-65, 70-80 are drawn to an antisense oligonucleotide "complementary" to at least "a portion" of a peripheral-type benzodiazepine receptor (PBR) gene "comprising" the nucleic acid sequence contained in SEQ ID NO: 1 or 2, and encoding the amino acid sequence of SEQ ID NO:3, wherein SEQ ID NO:3 comprises the mutant residues threonine 147 and arginine 162. Said antisense oligonucleotide, when introduced into a cell line that expresses PBR gene inhibits the

expression thereof, and thereby inhibiting proliferation of said cell line. The antisense oligonucleotide possesses a "complementary structure to at least a portion" of the nucleic acid sequence contained in SEQ ID NO:1 or 2. The antisense oligonucleotide possesses a size ranging from 7 to 40 nucleotides. The antisense oligonucleotide "comprises" the nucleotide sequence of SEQ ID NO:1 or 2, which inhibits the proliferation of a human breast cancer cell containing the PBR of SEQ ID NO:3.

It is noted that a portion could be of any size, including a few nucleotides, and that a complement could be partial or complete complement, wherein a partial complement could share with the gene comprising SEQ ID NO:1 or 2 only a few complementary nucleotides.

Thus, except for SEQ ID NO:1 or 2 of 650 bp each in length, the claimed antisense oligonucleotide, that could inhibit expression of PBR gene, encompasses small fragments of any sizes, including those from 7 to 40 nucleotides in length, the structure of which is not disclosed in the specification.

In other words, other than SEQ ID NO:1 or 2, **the structure of the small antisense oligonucleotides, such as those small fragments of 7 to 40 nucleotides, that could inhibit expression of the PBR gene is not disclosed.**

Further, It is noted that **SEQ ID NO:1 or 2 is only a cDNA fragment** encoding the mutated PBR polypeptide of SEQ ID NO:3 having mutation at threonine 147 and arginine 162, **and not a full length PBR coding sequence**.

Due to the language "comprising", **the genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2 encompass any nucleic acid containing SEQ ID**

NO:1 or 2, wherein said nucleic acid could have any sequences attached to the defined fragment, SEQ ID NO:1 or 2, provided it is in frame with SEQ ID NO:1 or 2. There is no limitation as to the nature of the molecules attached to SEQ ID NO:1 or 2. The present claim encompasses full-length genes and cDNAs that are not further described.There is substantial variability among the species of DNAs encompassed within the scope of the claims because SEQ ID NO:1 or 2 is only a fragment of any full-length gene or cDNA species. "A gene or an oligonucleotide comprising SEQ ID NO:1 or 2" encompasses a variety of subgenera with widely varying attributes .For example,a cDNA 's principle attribute would include its coding region.A partial cDNA that did not include a disclosure of any open reading frame (ORF)of which it would be a part,would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed.

Although the specification discloses a single cDNA fragment consisting of SEQ ID NO:1 or 2, this does not provide a description of a gene or an oligonucleotide "comprising" the nucleotide sequence of SEQ ID NO:1 or 2, and encoding a polypeptide fragment of SEQ ID NO:3.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like

a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of antisense oligonucleotides that could inhibit PBR expresssion, or a gene or an antisense oligonucleotide comprising SEQ ID NO:1 or 2, per Lilly by structurally describing a representative number of antisense oligonucleotides that could inhibit PBR expresssion, or a representative number of genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe antisense oligonucleotides that could inhibit PBR expresssion, or genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any antisense oligonucleotides that could inhibit PBR expresssion, or any genes or any antisense oligonucleotides comprising SEQ ID NO:1 or 2, other than SEQ ID NOs:1 and 2, nor any physical or chemical characteristics of antisense oligonucleotides that could inhibit PBR expresssion, or genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, other than SEQ ID Nos: 1 and 2, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID Nos: 1 and 2, this does not provide a description of antisense oligonucleotides that could inhibit PBR expresssion, or genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, that would satisfy the standard set out in Enzo.

The specification also fails to describe antisense oligonucleotides that could inhibit PBR expresssion, or genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, by the test set out in Lilly. The specification describes only SEQ ID NOs:1 and 2. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of antisense oligonucleotides that could inhibit PBR expresssion, or genes or antisense oligonucleotides comprising SEQ ID NO:1 or 2, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 53-57, 64-65, 74-75, 77-80 are rejected under 35 USC 112, first parargraph.

A. Claims 53-57, 64-65 remain rejected under 35 USC 112, first parargraph, for **lack of enablement for an antisense oligonucleotide "that inhibits PBR expression", wherein said antisense is "complementary to a portion" of a gene comprising SEQ ID NO:1 or 2**, for reasons already of record in paper of 01/28/04.

New claims 74-75, 77-80 are rejected for the same reasons of record.

Applicant argues that the amended and new claims are directed to relatively large oligonucleotides that comprise SEQ ID NO:1 or 2. Applicant recites Ellis et al, Waki et al, Rutka et al, and Resnicoff et al, all teaching that vector-mediated expression of a large cDNA complementary to a target gene in a mammalian cell inhibits the expression of the target gene.

The recitation of Ellis et al, Waki et al, Rutka et al, and Resnicoff et al is acknowledged and entered.

Applicant's arguments in paper of 09/30/04 have been considered but are found not to be persuasive for the following reasons:

It is noted that a portion could be of any size, including a few nucleotides, and that a complement could be partial or complete complement, wherein a partial complement could share with the gene comprising SEQ ID NO:1 or 2 only a few complementary nucleotides.

Thus, contrary to Applicant arguments, **the amended claims 53-57, 64-65 encompass antisense oligonucleotides of "any sizes, including small fragments, such as those of 7 to 40 nucleotides in length"**, that are complementary to at least a portion of a full length gene encoding PBR, comprising the polynucleotide fragment of SEQ ID NO:1 or 2, and **wherein said oligonucleotides inhibit proliferation of a cell line or a breast cell line that expresses said PBR gene.**

Further, n**ew claims 74-75, 77-80 encompass antisense oligonucleotides of any sizes, including small fragments, such as those of 7 to 40 nucleotides in length,** that are complementary to at least a portion of a full length gene encoding PBR comprising SEQ ID NO:3, **wherein said oligonucleotides inhibit proliferation of a cell line or a breast cell line that expresses said PBR gene, or inhibits proliferation of a mammalian cell.**

The specification discloses that SEQ ID NO:1 and 2 are partial cDNA sequences of PBR identified in breast cancer cell lines MDA-231 and MCF-7, respectively (p.15), wherein the breast cancer cell line MDA-231 is more aggressive, and expresses PBR at higher level than the non-aggressive cell line MCF-7 (page 36 and table 1 on page 36). The specification further discloses that the region surrounding the translation site and 5' to the translation has not yet been obtained (p.16, lines 7-10).

It is noted that the mutated SEQ ID NO:1 or 2 is only a fragment the mutated PBR gene, and that the structure of the full length sequence of said mutated PBR gene, including the region surrounding the translation site and 5' to the translation, and the 3' region, could not be predicted (Harris et al, J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Since the position of the active small antisense sequence, such as those having 7 to 40 nucleotides, on a gene could not be predicted, as taught by US 5,585,479, of record, one cannot predict whether the cDNA fragment consisting of SEQ ID NO:1 or 2 contains small nucleotide fragment(s) responsible for inhibition of the PBR expression.

Other than the full length SEQ ID NO:1 or 2, the specification has not taught whether and which small fragment(s) of SEQ ID NO:1 or 2, such as those of 7 to 40 nucleotides in length, could inhibit PBR expression.

Thus although the full length mutated SEQ ID NO:1 and 2, which are relatively large pieces of cDNA (650 bp), potentially could inhibit PBR expression, and although the wild type PBR gene sequence is known, however, since the structure of the mutated, full length mutated PBR gene comprising the mutated SEQ ID NO:1 or 2 is not known, and since one cannot predict that the active small antisense sequence(s), such as that of 7 to 40 nucleotides, is within the cDNA fragment consisting of SEQ ID NO:1 or 2, in view that the position of the active antisense sequence on a gene could not be predicted, as taught by US 5,585,479, of record, it would be undue experimentation for

one of skill in the art to make the claimed antisense oligonucleotide sequence that could inhibit expression of the mutated PBR gene.

B. If Applicant could overcome the above 112, first paragraph, Claim 65 still remains rejected under 35 USC 112, first paragraph, for **lack of enablement for an antisense oligonucleotide that inhibits "in vivo cell proliferation"**, as contemplated, for reasons already of record in paper of 01/28/04.

New claims 74-80 are rejected for the same reasons of record.

Claim 65, and new claims 74-80 encompass an antisense oligonucleotide that inhibits in vivo cell proliferation, as contemplated.

Applicant argues that the amended and new claims are directed to relatively large oligonucleotides that comprise SEQ ID NO:1 or 2. Applicant recites Ellis et al, Waki et al, Rutka et al, and Resnicoff et al, all teaching that vector-mediated expression of a large cDNA complementary to a target gene in a mammalian cell inhibits the expression of the target gene.

The recitation of Ellis et al, Waki et al, Rutka et al, and Resnicoff et al is acknowledged and entered.

Applicant's arguments in paper of 09/30/04 have been considered but are found not to be persuasive for the following reasons:

It is unpredictable that the claimed antisense oligonucleotide could be successfully used *in vivo*, as contemplated, because although the art teaches that some antisenses could inhibit expression of target genes in vivo, the behavior and effect of antisense oligonucleotide in vivo is not predictable, and even if the biological significant

amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss (of record). Similarly, Branch, AD, 1998 (of record) teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p50, first column).

Thus given the unpredictability of the behavior and effect of antisense oligonucleotide in vivo, it is unpredictable that the claimed antisense oligonucleotide would inhibit or reduce the expression of PBR in vivo in mammary gland, and thus one would not know how the use the claimed antisense oligonucleotides for in vivo expression as contemplated.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

December 06, 2004